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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Andrew VAILLANT et al.
Serial Number:	10/661,088
Filing Date:	September 12, 2003
For:	ANTIVIRAL OLIGONUCLEOTIDES TARGETING HBV
Art Unit:	1648
Examiner:	Bo, PENG
Agent:	Cawthorn, Christian

DECLARATION UNDER 37 C.F.R. SEC. 1.132

I, Jean-Marc Juteau, do hereby declare and state as follows:

1. I received the degrees of Bachelor (B.Sc.) of Biology from Montreal University in 1985, Master (M.Sc.) of Microbiology and Immunology from Montreal University in 1988, and Doctor of Philosophy (Ph.D.) of Microbiology and Immunology from Laval University in 1991.
2. My academic background and experiences in the field of the present invention are listed on the enclosed *curriculum vitae*.
3. I am a founder since 1999 of REPLICor Inc. and Senior Vice President since 2002.
4. I am an author of several scholarly publications as listed in my enclosed *curriculum vitae*.

5. I am an inventor in the present application; I have read and am thoroughly familiar with the contents of U.S. Patent Application Serial No 10/661,088 entitled "ANTIVIRAL OLIGONUCLEOTIDES TARGETING HBV", including the claims.
6. I have also read and understood the latest Official Action from the PTO dated May 2, 2006. In this Office Action, claims 3-32 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which is not described in the specification.
7. The following experiments had been performed under the supervision of Andrew Vaillant (inventor on this invention) and myself, to obtained results showing the *in vitro* antiviral activity of sequence independent oligonucleotides of the present invention against hepatitis B viruses (HBVs). These *In vitro* assays of viral infection are standard assays that can be used for the demonstration of an antiviral activity. These results cover different oligonucleotides (ONs).

   The following experiments were conducted to evaluate the antiviral activity occurring by a non-sequence complementary mode of action of oligonucleotides against HBV.

   REP 2006 (40mer PS-randomer) and REP 2004 (20mer PS-randomer) ONs were incubated with duck HVB (dHBV) during infection with primary duck hepatocytes. 96 hours after infection, dHBV infection was monitored by fluorescence microscopy using a dHBV surface antigen antibody. Antiviral

activity was scored as number of fluorescent plaques (groups of adjacent surface antigen positive cells arising from a focal infection of a single cell). IC50 was determined by a 50% reduction in the number of fluorescent plaques relative to the untreated control infected primary duck hepatocytes as shown in Table 1.

Table 1
Antiviral activity of REP 2006 and REP 2004

Compound	IC50 (uM)
REP 2004	0.133
REP 2006	0.127

In another experiment, REP 2006 (40mer PS-randomer) and REP 2031 (40mer PS-polyC) ONs were incubated with dHBV during and after infection of primary duck hepatocytes. dHBV infection was monitored by fluorescence microscopy using a DHBV core antigen antibody. Antiviral activity was scored as number of fluorescent (dHBV core antigen positive) cells. IC50 was determined by a 50% reduction in the number of fluorescent cells relative to the untreated control infected primary duck hepatocytes as shown in Table 2.

Table 2
Antiviral activity of REP 2006 and REP 2031

Compound	IC50 (uM)
REP 2006	< 0.01
REP 2031	< 0.001

In another experiment, the 2.2.15 hepatocyte cell line is permanently transfected with the human HBV (hHBV) genome and produces viral particles that do not reinfect the cell monolayer. Thus, this assay assesses a particular compounds ability to inhibit the production of hHBV virions. Virus production in the supernatant is monitored by quantitative RT-PCR (Taqman®). REP 2006 activity was assessed in the wild type as well as SM1 (pencyclovir resistant) and DM2 (lamivudine resistant) variants as shown in Table 3.

Table 3
Antiviral activity of REP 2006 in SM1 and DM2 variants

Strain	REP 2006 IC50 (uM)
Wild type	0.04
SM1 (pencyclovir resistant)	0.01
DM2 (lamivudine resistant)	0.007

These results show that ONs of this invention are effective antiviral agents against HBV.

8. The results presented hereinabove and produced according to the teaching of the present invention clearly proves that at least 3 different oligonucleotides of more than 10 nucleotides long as claimed in the present application are effective antiviral agents against HBV.

9. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by a fine or imprisonment, or both (18 U.S.C. Sec. 1001), and may jeopardize the validity of the application of any patent issuing thereon.

Signed  Dated: November 1, 2006

Jean-Marc Juteau

Curriculum vitae

JEAN-MARC JUTEAU, Ph.D

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Age: 42

Status: Married, three kids

Language spoken and written: French and English

EXPERIENCE

01-2002 - today
Senior Vice-President and Founder, REPLICor Inc., Laval.
Biopharmaceutical company developing antiviral and anticancer drugs.

Responsibilities:
- Science development
  Day to day contact with CSO, scientific input.
- In charge of intellectual property portfolio.
  Patent writing, strategy, management.

02-1999 – 01-2002
CEO and founder, REPLICor Inc., Laval.

Responsibilities:
- Science development
- In charge of financing
  Instrumental in raising $2.5M in equity and loan
- In charge of licensing and contract agreement
  Negotiation of licenses and contracts with universities

02-1996 to 02-1999
Officer, Office of Technology Transfer, McGill University, Montreal.

Responsibilities:
- Agreement management and negotiation
  License, research, option, confidentiality, material distribution.
- Spin-off company projects
  Set-up of spin-off company, contact with investors, business plan.

03-94 to 02-96
Product Manager, Iso Tech Design, Laval
Company developing and marketing micro-environments for pharma applications.

Responsibilities:

- Microbiology quality control..
- Distributor formation
  Contacts: Baxter Health Care, VWR, Khulman Tech., E.S.I. FluFrance, Liberty Clean Rooms, Millipore.

91 à 10-93
Director and Co-founder, DIAGNOGENE inc., R&D in biotechnology, Ste-Foy
Responsibilities: Financial and research administration, representation.

RESEARCH TRAINING

09-92 à 11-93
Post-doctoral scientist, **INRS-santé**, Pointe-Claire
Project: In-vitro mutagenesis of 4-chlorobenzoate dehalogenase in *Pseudomonas sp.* CBS3.

08-91 à 09-92
Post-doctoral scientist, **Institut de Recherches Cliniques de Montréal**
Project: Cloning et characterization of a cardiac specific transcription factor.

11-90
Training in molecular modeling, Department of Molecular and Cell Biology, **University of Connecticut.**

05-88 to 06-88
Workshop on DNA technologies: Sequence and in-vitro mutagenesis, **University of North-Carolina**, Chapel Hill, NC.

EDUCATION

87-91
Doctorate (Ph.D)., Microbiology and Immunology, **Laval University.**
Molecular biology, epidemiology and structure-function analysis of the ROB-1 ß-lactamase.

85-87
Master (M.Sc)., Microbiology and Immunology, **Montreal University and Hôtel-Dieu Hospital.**
Granulocytar function in recurrent vaginitis.

82-85
Bachelor (B.Sc.)., Biology, **Montreal University.**

BOARD MEMBERSHIP

2005- today
Member of the Montreal Life Science Committee.

2004- today
President of the Alumni Association of Montreal Clinical Research Institute.

SCHOLARSHIP, AWARD and PRIZES

Industrial Design Prize 1995 from the Design Institute (received in team for a micro-environment)
Institut National de la Recherche Scientifique (INRS) Fellowship, 1992-93.
Medical Research Council (MRC)Fellowship, 1992.
Fonds de la Recherche en Santé du Québec (FRSQ) Studentship, 1989-90-91.
Fonds pour la Formation des Chercheurs et l'Aide à la Recherche (FCAR) Studentship, 1988-89.
Canlab Prize from l'Association des Microbiologistes du Québec, 1989.

AUTHORSHIP

Patent filings:	20
Scientific articles:	10
Posters and oral presentations:	30

Vaillant A, Juteau JM, Lu H, Liu S, Lackman-Smith C, Ptak R, Jiang S. Phosphorothioate oligonucleotides inhibit human immunodeficiency virus type 1 fusion by blocking gp41 core formation. Antimicrob Agents Chemother. 2006 Apr;50(4):1393-401.

Kocisko DA, Vaillant A, Lee KS, Arnold KM, Bertholet N, Race RE, Olsen EA, Juteau JM, Caughey B. Potent antiscrapie activities of degenerate phosphorothioate oligonucleotides. Antimicrob Agents Chemother. 2006 Mar;50(3):1034-44.

Moaddel R, Price GB, Juteau JM, Leffak M, Wainer IW. The synthesis and initial characterization of an immobilized DNA unwinding element binding (DUE-B) protein chromatographic stationary phase. J Chromatogr B Analyt Technol Biomed Life Sci. 2005 Jun 25;820(2):197-203.

Sylvestre M, Sirois M, Hurtubise Y, Bergeron J, Ahmad D, Shareck F, Barriault D, Guillemette I, Juteau Sequencing of Comamonas testosteroni strain B-356-biphenyl/chlorobiphenyl dioxygenase genes: evolutionary relationships among Gram-negative bacterial biphenyl dioxygenases.Gene. 1996 Oct 3;174(2):195-202.

Ahmad D, Fraser J, Sylvestre M, Larose A, Khan A, Bergeron J, Juteau JM, Sondossi M. Sequence of the bphD gene encoding 2-hydroxy-6-oxo-(phenyl/chlorophenyl)hexa-2,4-dienoic acid (HOP/cPDA) hydrolase involved in the biphenyl/polychlorinated biphenyl degradation pathway in Comamonas testosteroni: evidence suggesting involvement of Ser112 in catalytic activity.Gene. 1995 Apr 14;156(1):69-74.

Juteau JM, Billings E, Knox JR, Levesque RC. Site-saturation mutagenesis and three-dimensional modelling of ROB-1 define a substrate binding role of Ser130 in class A beta-lactamases. Protein Eng. 1992 Oct;5(7):693-701.

Maclean IW, Slaney L, Juteau JM, Levesque RC, Albritton WL, Ronald AR. Identification of a ROB-1 beta-lactamase in Haemophilus ducreyi. Antimicrob Agents Chemother. 1992 Feb;36(2):467-9.

Juteau JM, Cote S, Levesque RC. Systematic site-saturation mutagenesis of ROB-1 beta-lactamase: efficiency of T4 polymerase and oligonucleotide synthesis. Biotechniques. 1991 Oct;11(4):460-2.

Juteau JM, Sirois M, Medeiros AA, Levesque RC. Molecular distribution of ROB-1 beta-lactamase in Actinobacillus pleuropneumoniae. Antimicrob Agents Chemother. 1991 Jul;35(7):1397-402.

Juteau JM, Levesque RC.Sequence analysis and evolutionary perspectives of ROB-1 beta-lactamase. Antimicrob Agents Chemother. 1990 Jul;34(7):1354-9.